FORM PTO-1390 (REV. 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
0471-0269P	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
10/018748 NEW	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/05621	June 19, 2000	June 22, 1999

TITLE OF INVENTION
THE USE OF THE PROTEIN UK 114 FOR INHIBITING ORGAN TRANSPLANT REJECTIOIN

APPLICANT(S) FOR DO/EO/US
BARTORELLI, Alberto; PANERAI, Alberto; NICOLETTI, Pierferdinando

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 00/78329 A2
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form PTO-1449(s), and International Search Report (PCT/ISA/210) with 4 cited document(s).
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    1.) Internatinal Preliminary Examination Report (PCT/IPEA/409)
    2.) Zero (0) Sheets of Formal Drawings

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531 Rec'd PCT/PT 21 DEC 2001

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
New 10/018748	PCT/EP00/05621	0471-0269P

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$1,040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	3 - 20 =	0	X **$18.00**	$ 0.00	
Independent Claims	2 - 3 =	0	X **$84.00**	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		none	+ **$280.00**	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1,020.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ 0.00	
SUBTOTAL =				$ 1,020.000	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 1,020.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00	
TOTAL FEES ENCLOSED =				$ 1,020.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ **1,020.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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Date: December 21, 2001

By #32,568
for Raymond C. Stewart, #21,066

/rem

PATENT
0471-0269P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: BARTORELLI, Alberto et al.

Int'l. Appl. No.: PCT/EP00/05621

Appl. No.: New Group:

Filed: December 21, 2001 Examiner:

For: THE USE OF THE PROTEIN UK 114 FOR INHIBITING ORGAN TRANSPLANT REJECTIOIN

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

December 21, 2001

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/EP00/05621 which has an International filing date of June 19, 2000, which designated the United States of America and was published in English.--

Docket No. 0471-0269P

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By #32868
for Raymond C. Stewart, #21,066

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RCS/rem
0471-0269P

THE USE OF THE PROTEIN UK 114 FOR INHIBITING ORGAN TRANSPLANT REJECTION

The present invention relates to the use of the protein UK 114 for reducing or inhibiting the rejection of organ transplants, as well as for maintaining transplant acceptance.

At present the continuous evolution of surgery techniques, together with the development of rather selective, more effective immunosuppressive drugs, have progressively improved the outcome of organ transplants.

However, organ transplantation as permanent solution in case of end-stage organ failure still suffers in practice from the severe problem of the rejection reaction. Treatment with immunosuppressive drugs is used to control such problem, with the consequence that infective complications are still the leading cause of death in transplant recipients. Furthermore, immunosuppressive therapy can never be stopped completely, even after resolution of any acute rejection, but it has to be continued as maintenance treatment indefinitely, although with relatively small doses.

The rejection of allografts (between genetically dissimilar members of the same species) can take place due to either a cell-mediated or a humoral immune reaction against the histocompatibility antigens (HLA) present on the membranes of the donor's cells.

The cell-mediated immune reaction causes graft destruction days to months after transplantation (**acute rejection**) and is characterized by progressive infiltration of mononuclear cells (macrophages, lymphocytes and monocytes) in the transplanted tissue; if these cells perceive antigen differences, they will activate T lymphocytes, which stimulate an immune response, both

cellular (T cells) and humoral (B cells) type, causing the destruction of the transplant. This type of cell-mediated rejection can often be treated with strong immunosuppressive therapy. In case of resolution, a novel acute rejection is unlikely to take place, and the allograft will usually survive for prolonged periods.

The role of humoral antibodies in rejection is clear when the recipient has been presensitized to the HLA antigens present in the graft: in these cases destruction of the transplanted organ takes place within a few hours or even minutes after the revascularization (**hyperacute rejection**).

Chronic rejection is a gradual process of deterioration and failure that occurs later in the life of the transplant, from several months to many years. The immunological mechanisms of the chronic rejection are less clear. The histological picture is different from that of acute rejection, and is characterized by lesions mainly on the arterial endothelium, where extensive proliferation gradually causes occlusion of the vessel lumen, ischemia and fibrosis of the graft.

Immunosuppressive treatment to control organ rejection is at present based on the use of corticosteroids, azathioprine (or cyclophosphamide in case of patients who do not tolerate azathioprine) and cyclosporin, often in a combination thereof.

However, each one of these medicaments involves a number of undesired side effects, which can be summarized as follows:

- corticosteroids: diabetogenicity, increase in proteins catabolism, adrenal cortex atrophy, reduction of the response of connective tissue to lesions, myopathy, osteoporosis, effects on the hematopoietic system and on nervous system);

- azathioprine: depression of bone marrow, hepatitis;
- cyclophosphamide: nefrotoxicity;
- cyclosporin: nefrotoxicity, hepatotoxicity, refractory hypertension and increase in neoplasias.

It is therefore evident the need for an alternative therapy preventing or reducing the rejection of a transplanted organ or tissue, or which anyway increases acceptance by the receiver without involving the above mentioned side effects.

It has now been found, and this is the object of the invention, that the protein having molecular weight of about 14 kDa in SDS-PAGE and obtainable by extraction from mammal liver with perchloric acid, disclosed in WO 97/30154 and in WO 96/02567 and known under the name UK 114, is capable of reducing or preventing rejection in allografts as well as maintaining the acceptance of the graft itself, without inducing the side effects typical of known immunosuppressive drugs.

The protein UK 114 acts on the immune system, exerting pleiotropic effects presumably due to a modulation of the cytokine production by T cells and macrophages.

According to the invention, the protein UK 114 of either extractive or recombinant origin will be administered parenterally, for example through the intramuscular, intravenous, intraperitoneal, subcutaneous, or sublingual routes.

Preferred formulation forms will be injectables forms, such as solutions or suspensions, sterile powders for the preparation of injectable solutions or suspensions; or solid forms such as tablets for the sublingual administration.

The protein of the invention may optionally be administered in combination with other conventional immunosuppressors, such as corticosteroids, azathioprine,

cyclophosphamide, cyclosporin, also in combination thereof.

The dose to be administered will depend on a number of factors, such as the individual characteristics of the patient (weight, etc.) as well as on the type of organ or tissue transplanted or intended for transplantation. In general, however, the amount of UK 114 to be administered will vary from 0.1 to 30 mg/kg/day for a time of 1 to 6 months after transplantation. After that, a maintenance treatment will be followed.

The administration procedures, such as dosage, administration route, duration of the attack and maintenance treatments, possible administration of known immunosuppressive or chemotherapic agents, either concomitantly or separately, will be defined by the skilled clinician.

The following example further illustrates the invention.

Example

Pancreatic islets transplantation in the mouse.

400 to 500 pancreatic islets were prepared from 5-6 week old euglycemic NOD mice, available from Charles River (Calco, Italy), and implanted under the renal capsule of female NOD mice suffering from spontaneous diabetes of recent onset (7-4 days) according to the procedure described by Mellgren A. et al., in Diabetologia, 1986, 29:670. This procedure allows to restore normoglycemia in NOD mice, followed by reappearance of hyperglycemia within 6-8 days, due to the destruction of the transplanted islets (see Sandberg J.O. et al., Clin. Exp. Immunol., 1997, 108:314).

Treatment with UK 114

Starting two days before transplantation, and subsequently every day for the duration of the experiment, three groups of 2-25 week old diabetic NOD mice (15

animals/group) were treated intraperitoneally with UK 114 at a dose of 30 or 60 μg/mouse (in 0.1 or 0.2 ml) or with 0.2 ml of PBS. Glycemia was measured in animals on days 3, 6, 9, 12 and 14 after transplantation from tail blood samples (ExacTech, Baxter Travenol, Deerfield, IL). The animals were considered diabetic when glycemia was higher than 11.8 mmol/l after 6 hour fast.

During the experiment one animal of the control group and another of the group treated with UK 114 at low dosage died on day 2 and 3 after transplantation and they were not considered in the calculation of data.

On day 3 of the experiment, 5/14 mice of the PBS-treated control group were still normoglycemic, on day 6 only one mouse of this group was normoglycemic, and on day 9 all animals were markedly hyperglycemic with glycemia mean values (SD) of 16.2 ± 3.2 mmol/l, which further increased to 18.9 ± 4.5 on day 14 (See table).

Conversely, treatment with UK 114 dose-dependently prevented reappearance of hyperglicemia in transplanted NOD mice. Of the animals treated with 30 μg of UK 114, 12/14 animals were normoglycemic on day 6 and 11 out of 14 on day 9 and 14 (See table). None of the 15 animals treated with the higher dosage of UK 114 became diabetic during the 14 days subsequent transplantation (See table).

These data prove that the administration of UK 114 can prevent, or anyhow delay, rejection of pancreatic islets in a well-known animal model and suggest the potential use of the treatment with UK 114 in the prevention of the rejection of transplanted pancreatic islets in IDDM patients.

TABLE

Days	3	6	9	14
PBS	9/14 diabetic [a]	13/14 diabetic [d]	14/14 diabetic [d]	14/14 diabetic [d]
UK 114 30 μg	2/14 diabetic [b]	3/14 diabetic [c]	3/14 diabetic [e]	3/14 diabetic [e]
UK 114 60 μg	0/15 diabetic [c]	0/15 diabetic [f]	0/15 diabetic [f]	0/15 diabetic [f]

b vs a, $p = 0.02$ with chi-square

c vs a, $p < 0.0001$ with chi-square

e, f, vs d, $p < 0.0001$ with chi-square.

CLAIMS

1. The use of the protein UK 114 for the preparation of medicaments for reducing or inhibiting organ the rejection of transplants and for maintaining the acceptance of the transplant itself.

2. The use as claimed in claim 1, for reducing or preventing the rejection of Langerhans cells transplants.

3. Protein UK 114 as anti-rejection agent.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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28 December 2000 (28.12.2000)

PCT

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MI99A001384 22 June 1999 (22.06.1999) IT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/78329 A2

(54) Title: THE USE OF THE PROTEIN UK 114 FOR INHIBITING ORGAN TRANSPLANT REJECTION

(57) Abstract: The use of the protein UK 114 for reducing or preventing the rejection of organ transplants, as well as for maintaining transplant acceptance.

Attorney Docket No.:
0471-0269P

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PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: The use of the protein UK 114 for inhibiting organ transplant...

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,
the specification was filed on _____ as
United States Application Number _____;
and amended on _____ (if applicable) and/or
the specification was filed on 19.06.2000 as PCT
International Application Number PCT/EP00/05621; and was
amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
MI99A001384 (Number)	Italy (Country)	22.06.1999 (Month/Day/Year Filed)	☒ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	☐ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	☐ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

Insert Provisional Application(s): (if any)

_____ (Application Number) _____ (Filing Date)

_____ (Application Number) _____ (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application Number	Date of Filing (Month/Day/Year)
_____	_____	_____
_____	_____	_____

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Insert Prior U.S. Application(s): (if any)

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
_____	_____	_____
_____	_____	_____

Attorney Docket No.:

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

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PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING: ↓

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor: Insert Name of Inventor →
Insert Date This Document is Signed
Insert Residence Insert Citizenship →
Insert Post Office Address →

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Full Name of Fifth Inventor, if any: see above

GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Residence (City, State & Country)		CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		

*DATE OF SIGNATURE